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Congenital Dyserythropoietic Anemias

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The congenital dyserythropoietic anemias (CDAs) are a group of relatively rare inherited anemias that share in common ineffective erythropoiesis and morphologic abnormalities of mature red blood cells and their precursors. Three major types of CDA and a number of variants have been described. The diagnosis and categorization of these disorders are facilitated by microscopic examination of the blood and bone marrow and by serologic testing. Management of patients currently consists of observation and supportive care. Because patients with CDAs may be at significant risk for secondary hemochromatosis, they require monitoring for this condition. Splenectomy may be of benefit in certain cases in which the anemia is particularly severe. Over the past few years advances have been made in understanding the pathogenesis of these disorders, and it now appears that CDA II results from enzymatic defects in the cellular glycosylation pathway. © 1996 Wiley-Liss, Inc.

Key words: anemia, dyserythropoiesis, HEMPAS, review

INTRODUCTION

The congenital dyserythropoietic anemias (CDAs) are a group of inherited disorders characterized by mild to moderate anemia, ineffective erythropoiesis, and morphologic abnormalities of mature red blood cells and their precursors. Only a few hundred cases of CDAs have been reported, and these anemias are therefore considered rare. However, because clinical and laboratory findings may be subtle, it is possible that many patients with CDAs have been unrecognized or have been misdiagnosed with other congenital or acquired forms of anemia.

Three types of CDA have been described (CDA I–III) as well as a number of variants. Classification is based on morphologic findings in the bone marrow in conjunction with serologic studies. Although the etiology of CDA II has apparently been defined at the molecular level, little is known about the mechanisms underlying the other forms. This review will outline the clinical and laboratory features of the CDAs, describe what is known about their pathogenesis, and offer some suggestions for patient management. The reader is referred to Ciba Foundation Symposium 37 and the text *Dyserythropoiesis* edited by Lewis and Verwilgen for more detailed descriptions of these disorders [1,2].

HISTORICAL BACKGROUND

Wolff and von Hofe are credited with the first clinical report of CDA in 1951. They described a mother and three children with mild anemia and unusual multinucleated erythroblasts in their bone marrows [3]. The term congenital dyserythropoietic anemia was subsequently introduced to emphasize the morphologic features of this condition and its apparent hereditary basis [4,5]. A number of subsequent cases describing similar yet distinct anemic syndromes prompted Heimpel and Wendt to propose a classification scheme for these disorders in 1968 [6–8]. Mainly on morphologic criteria, they divided the CDAs into types I, II, and III. Shortly thereafter, Crookston and co-workers noted an unusual laboratory finding in patients with CDA II: peripheral red blood cells were lysed by a percentage of ABO-compatible normal sera in the acidified-serum lysis test (Ham test) [9]. For this reason CDA type II became known as hereditary erythroblastic multi-

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TABLE I. Distinguishing Features of the Three Main Types of Congenital Dyserythropoietic Anemia

Characteristics	CDA I	CDA II	CDA III
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal dominant, sporadic cases (? new mutations)
Physical examination	Splenomegaly	Jaundice, splenomegaly, hepatomegaly	None
Hb concentration	Mild to moderate decrease	Mild to moderate decrease	Mild decrease
Mean corpuscular volume (MCV)	Mild to moderate increase	Normal to mild increase	Normal to mild increase
Bone marrow			
Light microscopy	Small population of binucleate cells (usually <10%), internuclear chromatin bridges	Multinucleated cells (usually 15–30%)	Gigantoblasts, multinuclear cells
Electron microscopy	Spongy appearance of nuclei, invasion of nuclear region by cytoplasm	Excess cisternae frequently adjacent to the plasma membrane	Clefts in nuclei, autolytic areas in cytoplasm
Serology			
Acidified-serum test	Negative	Positive	Negative
Anti-i and anti-I agglutinability	Slight	Strong	Variable

nuclearity associated with a positive acidified-serum test (HEMPAS). Although originally thought to be concentrated in the Baltic and Mediterranean basin regions, CDAs have now been described in patients of diverse ethnicity in North and South America, Africa, Australia, and Asia [10].

FEATURES COMMON TO ALL CDAs

There is a wide range in the severity of the anemia observed in the CDAs: some patients are completely asymptomatic, whereas others may require blood transfusion. Most commonly, however, the anemia is mild to moderate, with hemoglobin (Hb) concentrations between 8 and 11 g/dl. Normocytic or macrocytic indicies are typical (Table I). Abnormalities of mature erythrocytes, including anisocytosis, poikilocytosis, anisochromasia, and punctate basophilic stippling, can be pronounced and may serve as the first clue to an underlying CDA. Reticulocytes are usually normal or slightly increased in number.

Bone marrow examination reveals marked erythroid hyperplasia, reversal of the myeloid to erythroid ratio, and a certain degree of red cell multinuclearity. Granulopoiesis and thrombopoiesis are generally unremarkable, although a few cases describing morphologic derangements in these cell lineages have been reported [11–13]. No specific chromosomal finding has been linked to the CDAs. However, analysis of the erythroblasts has frequently revealed them to be hyperdiploid. This is consistent with the occurrence of ineffective cell division leading to an increased complement of chromosomes within the cells [14].

Features of ineffective erythropoiesis, including shortened half-life of plasma iron clearance and increased plasma iron turnover, are prominent. The red cell half-life is decreased to a variable extent in these disorders. Hyperabsorption of iron from the gastrointestinal tract frequently leads to secondary hemochromatosis except in those patients protected by ongoing iron loss (e.g., menstruation or hemosiderinuria) [15,16]. Transferrin saturation, ferritin levels, and stainable iron in the bone marrow are often increased, but ringed sideroblasts are rarely, if ever, detected. Typical of ineffective erythropoiesis, hemolysis occurs predominantly in the medullary space; elevation of serum lactate dehydrogenase and unconjugated bilirubin along with depression of serum haptoglobin are frequently noted, most consistently in CDA II. A small component of red cell destruction may occur in the spleen, as evidenced by the response to splenectomy in a number of patients [17–19]. In addition, imbalances in globin chain synthesis have been described in occasional cases of CDA I and CDA II [20,21]. The etiology of the globin chain imbalances is unknown; however, they likely represent a secondary, rather than primary, phenomenon.

SPECIFIC FEATURES OF CDA I

Based on more than 60 reported cases, the pattern of inheritance of CDA I is autosomal recessive. Although variation in clinical expression has been well documented, most patients present with splenomegaly and mild to moderate macrocytic anemia (Table I) [22]. Cabot rings, observed in circulating erythrocytes, appear to be unique to CDA I [23]. Recently, CDA I has been associated with skeletal abnormalities of the limbs in two unrelated patients who presented with a lack of distal phalanges and nails as well as syndactyly, similar to defects observed in Fanconi's and Diamond-Blackfan anemias [24]. The finding of further cases will be required, however, before the strength of this association can be determined.

Under light microscopy, a small percentage of erythro-

blasts (usually 5–10%) are either binucleate or contain an irregular nuclear mass resulting from incomplete nuclear division (Fig. 1a). These nuclei may be of different size and staining characteristics [15]. In a limited number of erythroid precursors, thin strands of chromatin connect the nuclei of cells that have otherwise completed division. These so-called internuclear chromatin bridges are most characteristically, but not exclusively, seen in CDA I.

Electron microscopy has further defined morphologic abnormalities in the marrow. Dyserythropoiesis seems limited to more mature red cell precursors since proerythroblasts and early basophilic erythroblasts appear normal [25]. Among the degenerative changes of the nucleus, the most characteristic is uneven condensation of chromatin, leading to a "spongy" nuclear configuration (Fig. 1b). The contour of the nuclear membrane may be interrupted by invaginations, resulting in the presence of cytoplasm and even organelles within the nuclear region [26]. Internuclear bridges as long as 12 μm have been described [27].

SPECIFIC FEATURES OF CDA II

By virtue of the fact that over 100 cases have been reported, CDA II is the most common of the three major types. Like CDA I, it is inherited as an autosomal recessive trait. Synonyms for this disorder include HEMPAS, familial benign erythroblastic polyploidy, and hemolytic-splenomegalic erythropolydyskaryosis [28].

Splenomegaly and jaundice are found in the majority of patients; hepatomegaly and gallstones are seen less frequently. A number of associations with CDA II have been reported, although each in only one or a few patients: mental retardation, Sweet's syndrome, von Willebrand's disease, and Dubin-Johnson syndrome among others [29–31]. Rather than being true associations, it seems more likely that the majority represent coincidental occurrence.

A significant but variable proportion of polychromatophilic and orthochromatic erythroblasts (usually 15–30%) are bi- or multinucleate in CDA II (Fig. 1c). Cells with more than four nuclei are relatively rare. Karyorrhexis is commonly observed. Pseudo-Gaucher cells may be present, representing the debris of ineffective erythropoiesis within the reticuloendothelial system [32,33].

Electron microscopy reveals redundant membrane within the cytoplasm of erythroblasts. These characteristic cisternae, usually found adjacent to the cell's outer membrane, appear to be composed of excessive smooth endoplasmic reticulum (Fig. 1d) [34]. They have been seen in 90% of erythroblasts and 2% of erythrocytes, suggesting that their presence does not interfere with normal maturation [35].

The most characteristic feature of CDA II is the finding that sera from a panel of ABO-compatible individuals causes hemolysis of erythrocytes in the acidified-serum lysis test. This phenomenon is generally observed with 30% of sera from normal individuals but can occur with a significantly smaller percentage [36]. IgM antibodies against abnormal cell surface components on CDA II red cells mediate this process, so the variation observed in the number of different sera causing hemolysis probably reflects the variable prevalence of these antibodies in normal individuals. A positive acidified-serum lysis test with heterologous sera is specific for CDA II and should be considered requisite for diagnosis (Table I).

The erythrocytes from patients with CDA II also exhibit an increased agglutinability and lysis to anti-i and anti-I sera. These surface antigens are complex carbohydrate structures found predominantly on fetal and adult red cells, respectively. The oligosaccharide structure of i is a linear chain, in contrast to that of I, which is branched [37]. Relatives of patients with CDA II who have normal marrows but increased agglutinability to anti-i appear to be heterozygote carriers of this disorder [38].

The distinction of CDA II from paroxysmal nocturnal hemoglobinuria (PNH) is facilitated by the acidified-serum lysis test and the sucrose hemolysis test. The erythrocytes in CDA II do not lyse with homologous serum as they do in PNH. In addition, the sucrose hemolysis test is negative in CDA II, whereas it is positive in PNH.

SPECIFIC FEATURES OF CDA III

CDA III is the rarest of the three major forms. Only 30 cases have been described, 15 of which were reported in a single Swedish family [39]. It is also known as familial erythroid multinuclearity and hereditary benign erythroreticulosis and is inherited as an autosomal dominant trait, although sporadic cases have also been described [40,41]. These latter cases may represent spontaneous dominant mutations [42]. The gene for CDA III has recently been localized to chromosome 15q21-q25 using linkage analysis on the large Swedish family described above [43]. In addition, though it is possibly a chance association, an excess number of cases of monoclonal gammopathy and myeloma have been described in this family [44].

In CDA III splenomegaly appears to be the exception rather than the rule (Table I) [45]. Giant erythroblasts with up to 12 nuclei are the most distinctive feature of CDA III observed on light microscopic examination of the bone marrow (Fig. 1e). Abnormally large lobulated nuclei and discordance in nuclear maturation are also found. While they are hallmarks of CDA III, these findings are not pathognomonic, since they may be seen in other rare disorders (e.g., erythroleukemia). Electron microscopy demonstrates nuclear clefts and autolytic areas within the cytoplasm (Fig. 1f) [46].

The acidified-serum lysis test is negative in CDA III. Agglutination and lysis of erythrocytes to anti-i antibody

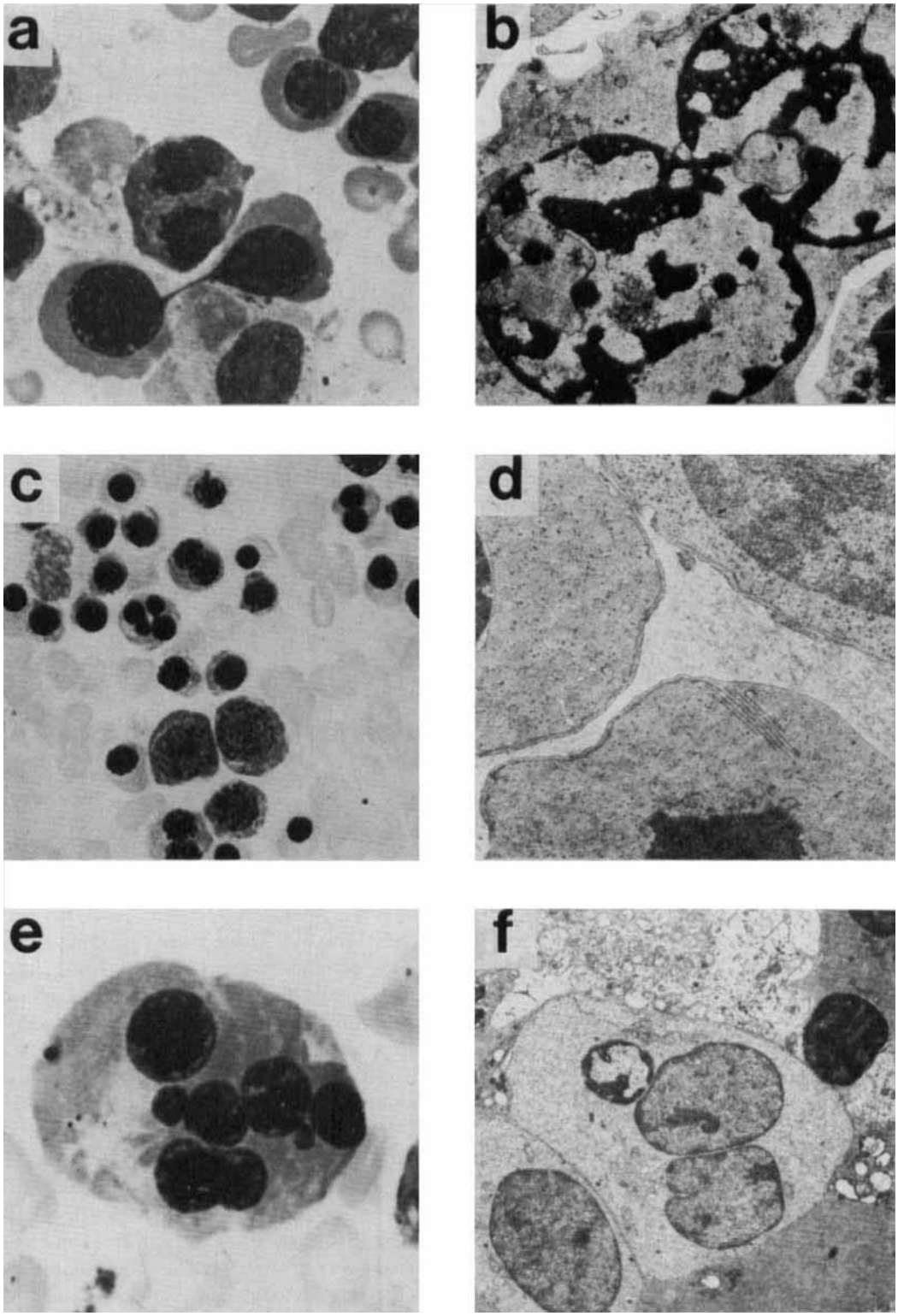

Fig. 1. The light and electron microscopic findings in the congenital dyserythropoietic anemias. a: Internuclear bridge remaining after cell division (CDA I). b: Spongy chromatin appearance in an incompletely divided nucleus (CDA I). c: Several multinucleated erythroblasts, in particular, one with four nuclei to the left of center (CDA II). d: Redundant cisternae present in the cytoplasm of an erythroblast (CDA II). e: Polychromatophilic erythroblast with many nuclei at different stages of maturation (CDA III). f: Multiple nuclei, one of which contains a cleft (CDA III). [Reprinted with permission from Heimpel [15,22] (a, b), Verwilghen [10] (c, d), and Goudsmit [45] (e, f).]

has only been examined in a few cases of CDA III, with conflicting findings [40,42].

FEATURES OF CDA VARIANTS

A number of CDA variants probably exist. McBride and others have proposed a separate category, CDA IV, to describe cases similar to CDA II, but lacking a positive acidified-serum lysis test [47,48]. Other reports describe forms of CDA that appear distinct because specific morphologic features are absent, because patterns of inheritance are different, or because of additional associated clinical data [49,50–52]. Occasionally, upon reexamination, these cases conform to the classification scheme established by Heimpel and Wendt. Reclassification of variants as CDA II is particularly common, usually because an insufficient number of sera were used in the initial acidified-serum lysis test [53,54]. Cases of CDA with more severe hematologic complications including hydrops fetalis have also been reported [55–57]. Although the number of CDA variants appearing in the literature may reflect improper categorization in some instances, variable penetrance or diverse molecular defects may also be responsible.

PATHOGENESIS OF THE CDAs

The defect in the CDAs is intrinsic to all erythroid progenitors rather than restricted to a subpopulation of cells [58–61]. Aside from limited biochemical data, which have mainly been descriptive, little more is definitively known about the pathogenesis of CDA I and CDA III [62–66].

By contrast, the pathogenesis of CDA II has been relatively well worked out. Early studies of erythrocytes from patients with this disorder identified abnormalities in membrane proteins and lipid composition. Glycoproteins on CDA II erythrocytes were found to have an abnormal carbohydrate structure, leading to aberrant reactivity with anti-i serale [67,68]. Increased glycolipids were also found in the red cell membrane [69]. Based on additional studies, it was suggested that the IgM antibody responsible for hemolysis in the acidified-serum lysis test recognizes an abnormal glycolipid structure sharing homology with the i and I antigens [70]. Thus, a variety of data have suggested that abnormalities in the glycosylation pathway might be involved in the etiology of CDA II.

Synthesis of cell surface membrane glycoproteins in part, entails the enzymatic addition of a mannose-rich core structure to asparagine residues identified by a specific amino acid sequence. Through the action of multiple enzymes found in the endoplasmic reticulum and Golgi apparatus, the core structure is repetitively truncated and

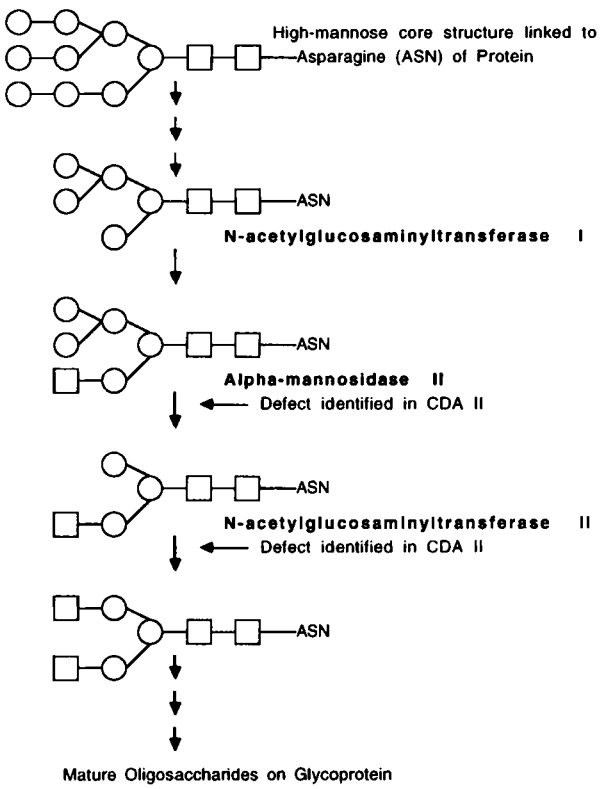

Fig. 2. Enzymatic defects of glycosylation in congenital dyserythropoietic anemia type II. Normally the production of asparagine-linked oligosaccharides proceeds by the addition of a high mannose-containing core structure, which is subsequently trimmed by the action of a number of enzymes. Two different enzymatic defects described in CDA II are depicted. Blockage of synthesis at the level of alpha-mannosidase II or N-acetylglucosaminyltransferase II leads to the presence of incompletely processed oligasaccharides on glycoproteins. Circles represent mannose residues, and squares represent N-acetylglucosamine.

elongated, eventually resulting in the production of a glycoprotein with mature oligosaccharides (Fig. 2).

Fukuda and co-workers have described two separate defects in this enzymatic pathway that occur in CDA II: alpha-mannosidase II deficiency and N-acetylglucosaminyltransferase II deficiency [71,72]. As a result of the former abnormality, addition of new sugar moieties to the oligosaccharide core structure is impaired. A defect, likely in the promoter region of the gene encoding for alpha-mannosidase II, has been identified, for the first time linking a molecular defect with a CDA. Low levels of N-acetylglucosaminyltransferase II, the enzyme responsible for addition of an N-acetylglucosamine residue to one of the arms of the core, also results in glycoproteins with truncated oligosaccharides (Fig. 2).

An additional enzymatic defect has been described in a case of CDA II with variant features. Low levels of the membrane-bound form of galactosyltransferase, involved

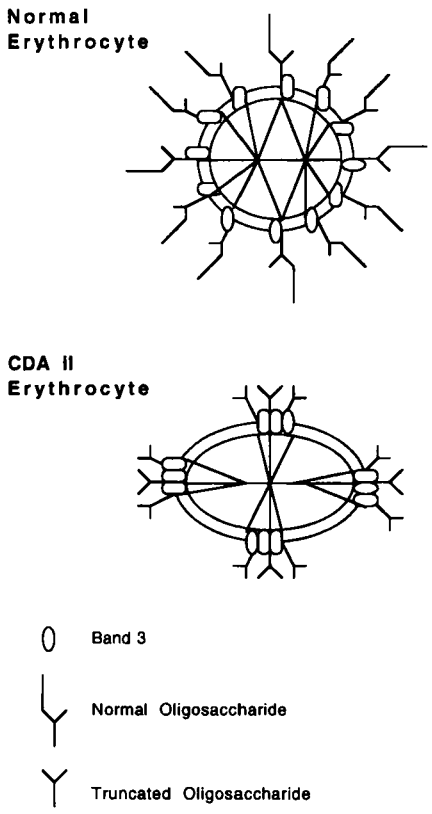

Fig. 3. Hypothetical model leading to the disruption of the cytoskeleton in CDA II. Normally, Band 3 is evenly distributed in the plane of the erythrocyte membrane. In CDA II erythrocytes, however, Band 3 may cluster. This could lead to disruption of the membrane skeleton and be responsible for premature cellular demise.

at various stages of oligosaccharide synthesis, severely affect processing and lead to the presence of primitive high-mannose core structures on glycoproteins [73].

The above enzymatic defects lead to abnormal oligosaccharides on major erythrocyte proteins such as the anion transporter Band 3 [74,75]. In addition to its other functions, this glycoprotein plays a critical role in the organization of the membrane skeleton that determines normal red cell strength, flexibility, and shape. Abnormal glycosylation of Band 3 may lead it to cluster on the cell surface [76] (Fig. 3). Such clustering could cause disruption of the structural network of the erythrocyte and its precursors, thereby leading to their premature demise.

Defective glycosylation on the red blood cell surface may affect other processes as well. Abnormalities in the regulation of complement have been identified on the surface of erythrocytes. Enhanced functional activity of the alternative pathway C3 convertase and of the membrane attack complex may result from the improper glycosylation of glycophorin A, which has been proposed to serve as a complement regulatory protein [77].

Cell lineages other than the erythroid are not affected to the same extent in CDA II because the glycoproteins on their surfaces contain different oligosaccharide structures that permit them to maintain features more like their normal counterparts [78]. However, as expected from the presence of a generalized enzymatic defect in glycosylation, studies have documented that secreted glycoproteins such as transferrin also contain incompletely processed oligosaccharides [79]. Such data indicate that the incomplete processing of glycoproteins may have functional consequences for processes other than erythropoiesis.

TABLE II. Differential Diagnosis of the Congenital Dyserythropoietic Anemias

Disease	Laboratory study
Megaloblastic anemia	Red cell folate, serum B_{12} levels
Myelodysplasia	Bone marrow examination with iron stain, cytogenetics
M6 acute myelogenous leukemia	Bone marrow examination with special histochemistry (periodic acid-Schiff stain)
Other congenital and acquired hemolytic anemias	
Thalassemia	Hb electrophoresis, molecular genetic analysis
Membrane cytoskeleton defects (e.g., hereditary spherocytosis)	Osmotic fragility, membrane protein analysis
Enzymopathies	Enzyme levels (e.g., pyruvate kinase)
Paroxysmal noctural hemoglobinuria	Acidified-serum test (positive with homologous serum), sucrose hemolysis test

DIFFERENTIAL DIAGNOSIS OF THE CDAs

The diagnosis of a CDA should be considered in patients of all ages, including newborns, who present with a normocytic or macrocytic anemia, particularly when anisocytosis and poikilocytosis is prominent [80,81]. Laboratory data consistent with hemolysis and the presence of iron overload alert the clinician to the possibility of ineffective erythropoiesis and strengthen the likelihood of a CDA. Examination of a bone marrow aspirate with light and electron microscopy help to identify and distinguish the various CDAs, but care must be taken in interpreting morphologic findings because overlap exists between disorders [82].

Once suspected, a number of laboratory studies are useful to eliminate other hematologic conditions potentially confused with the CDAs (Table II). Red cell folate and serum vitamin B_{12} levels help rule out megaloblastic anemia. Morphologic abnormalities of the granulocytic and megakaryocytic lineages, ringed sideroblasts, and cytogenetic abnormalities characterize subsets of myelodysplasia. In erythroleukemia (M6 acute myelogenous leukemia), pancytopenia is typically present and the erythroblasts are periodic acid-Schiff (PAS) stain positive.

Hemoglobinopathies are in part eliminated from consideration by a carefully interpreted hemoglobin electrophoresis, although more detailed studies may be necessary. Hereditary spherocytosis and other disorders affecting the red cell membrane skeleton are identified by increased osmotic fragility and by membrane protein analysis [83]. Biochemical assays can be employed to exclude enzymatic defects.

MANAGEMENT OF PATIENTS

Anemia is often mild and requires no intervention. If anemia is more severe, splenectomy may be of benefit in the CDAs. The most experience showing a benefit from this procedure has been in CDA II, and the benefit of splenectomy in CDA I is more controversial [17–19]. In any case, prior to undertaking surgery, erythrokinetic studies can be performed to quantitate the extent of peripheral red blood cell destruction.

Standard hematinics are of no use in the treatment of CDA itself. In particular, iron therapy is almost always contraindicated because of the strong predisposition of patients to develop iron overload. For this same reason, blood transfusions should be minimized. In this regard, most patients with CDAs do not require regular transfusion therapy. However, blood transfusion may become necessary in certain instances. For example, as with other hemolytic syndromes, patients with CDAs are susceptible to aplastic crises precipitated by infection with parvovirus or other pathogens [84].

Asymptomatic extramedullary hematopoiesis has been reported and may mimic tumors of the mediastinum, abdomen, and vertebral column [85,86]. Because of the increased red cell production which occurs, the development of sites of extramedullary hematopoiesis may result in an amelioration of the degree of anemia [87]. Technetium-99m sulfur colloid scintigraphy may be useful in delineating the extent of these regions [86].

It appears that patients with CDAs are predisposed to hepatic cirrhosis, irrespective of their body iron burden. The factors responsible for this have not been identified conclusively but may relate to the constant clearance of abnormal proteins by the liver [79]. One of the more important issues in the management of the CDAs is therefore the avoidance of iron overload and secondary hemochromatosis exacerbating this tendency [88,89]. CDA has been diagnosed retrospectively after autopsy when death was in part caused by heart failure secondary to iron overload [90]. Blood transfusion should be avoided unless absolutely necessary, and patients should be routinely monitored for evidence of iron overload. Although no clinical trial has examined the use of deferoxamine in the CDAs, a case report has appeared in which it was used successfully to reduce the iron burden [91]. Given that iron overload is likely to be particularly harmful in this condition, deferoxamine therapy should be considered in the management of these patients after documentation of tissue iron overload and careful consideration of its benefits and risks.

Once an index case of CDA has been defined, it is important to identify family members who may not know they are affected. Even if they are asymptomatic from the perspective of their anemia, monitoring for iron overload may be of benefit. In addition, genetic counseling may play a role, particularly in countries with a high rate of consanguineous marriage. Although one molecular defect underlying CDA II has been identified, future studies are likely to elucidate the pathogenesis of the other types and make diagnosis possible at the molecular level.

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